Leukemia

Duration of Life in Children Treated with Corticotropin and Cortisone

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• *The average duration of survival of 15 cases of childhood leukemia treated with corticotropin and cortisone was 6.8 months. This survival was the same as observed among 59 children who received no treatment, or treatment with x-ray, or blood transfusion alone.*

Despite the fact that objective evidence of remission was observed in 7 of 15 children treated with corticotropin and cortisone, the remissions were not reflected by a longer duration of life.

Treatment of childhood leukemia with corticotropin and cortisone appears to be a palliative measure, without significant effect on the duration of life.

IN THE THERAPEUTIC trials of corticotropin (ACTH) and of cortisone for neoplastic diseases, particular interest and emphasis have been manifested in their use in children with leukemia.[2, 3, 4] A recent summation[4] recorded the experience from eight clinical research centers. Of 218 children with leukemia treated with corticotropin or cortisone either alone or in combination with other therapy, 98 or 45 per cent were reported to have had objective evidences of clinical remission of the disease. The length of the remissions was from one to ten weeks. When subsequent courses of hormonal therapy were given, only a few of the patients had beneficial responses.

Few reports have emphasized the duration of life in patients treated with these hormones. This information would appear to be crucial for the evaluation of the effectiveness of the agents in leukemia, whether such evaluation is used for research or for practical therapeutic purposes.

In the present study of fifteen children with leukemia treated with corticotropin and cortisone it was noted that although there was objective as well as subjective evidence of clinical improvement, these manifestations were not reflected in a statistically significant prolongation of life.

PATIENTS AND METHODS

The diagnosis in all cases was supported by at least two examinations of aspirated bone marrow and by classical clinical and hematologic symptoms.

Corticotropin (adrenocorticotropic hormone or ACTH) and cortisone (17-hydroxy-11-dehydrocorticosterone)† were administered intramuscularly, usually in divided doses at 6- to 8-hour intervals. The daily dose varied from 25 mg. to 300 mg. Courses of ten days or more were followed by a rest period of seven to ten days before the alternative hormone was instituted.

All patients were on a low-salt diet (less than 1.0 gm. of sodium chloride per day) to prevent edema, and when practicable supplemental oral potassium chloride was administered to avoid hypokalemia. Supportive therapy with both antibiotics and blood transfusions was used in 12 of the 15 cases.

Examination of the patients, as well as determination of the content of hemoglobin, erythrocytes, leukocytes and platelets in the blood, was carried out at least twice a week, and more often when indicated. Studies of the chemical constituents of the blood were performed only for the proper care of the patient.

Table 1 presents the relevant data regarding the 15 children. Fourteen died, and autopsies confirming the diagnosis of lymphoblastic leukemia were available in 12. One patient (Case 4), who was alive more than two years after onset, had mild generalized adenopathy, and the predominant abnormal lymphocytes in the peripheral blood and bone marrow aspirate were consistently of the small, mature type. During the second year of the disease a few cervical nodes were enlarged and the spleen was barely palpable. The case must be considered one of chronic subleukemic lymphogenous leukemia.

Of the 14 patients who died, five (Cases 2, 3, 7, 12 and 14) were subleukemic during the course of the disease. Five patients (Cases 6, 9, 10, 11 and 13) had frank leukemia, with leukocytes numbering 20,000 to 500,000 per cu. mm. of peripheral blood. Four patients (Cases 1, 5, 8 and 15) had both leukopenia and leukocytosis during the course of illness.

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†Obtained from the Armour Laboratories and Merck and Company, respectively, through the National Institutes of Health.

TABLE 1.—*Effects of Corticotropin and Cortisone in Children with Leukemia.*

Case	Sex	Age	Duration Prior to Course (Mos.)	Hormone	Total Dose (Mg.)	Days Treated	Previous Therapy	Antibiotics	Blood Transfusions	Subjective Improvement	Decreased Spleen Size	Decreased Adenopathy	Decreased Liver Size	Decreased Fever	Decreased Leukemic Cells—Peripheral	Decreased Leukemic Cells—Bone Marrow	Increased Platelets	Duration of Effects (Wks.)	Survival from Onset (Mos.)
1.	M	1.5	1	Cort.	1,650	36	....	Yes	2	*	*	*	*	*	*	*	*	7	
			3	ACTH	1,050	18		....	....	*	*	0	0	0	†	0	—	2	
			4	Cort.	250	10		....	....	*	0	0	0	—	—	0	0	—	
			5	ACTH	625	13		Yes	2	—	—	—	—	—	—	—	—	—	6.0
2.	F	11	4	ACTH	1,700	14	....	....	2	*	—	—	—	*	—	—	0	—	
			5	Cort.	1,700	14		Yes	4	*	*	*	*	*	*	*	0	16	
			8	ACTH	1,700	14		Yes	....	*	—	—	—	0	—	—	0	—	
			9	Cort.	1,400	14		Yes	5	*	—	—	—	—	—	0	0	—	11.0
3.	M	3	2	Cort.	1,025	11	....	Yes	2	*	*	*	*	0	*	0	†	2	
			2.5	ACTH	600	12		Yes	....	*	0	0	0	0	*	0	†	2	
			3	Cort.	375	11		Yes	....	*	0	0	0	*	—	0	—	—	
			3.5	ACTH	350	15		Yes	....	—	—	—	—	*	—	0	—	—	
			4	Cort.	700	7		Yes	3	—	—	—	—	—	—	—	—	—	5.0
4.	M	2	5	Cort.	1,550	31	....	Yes	....	0	0	*	0	0	—	†	0	—	
			6.5	ACTH	500	10		....	....	*	0	0	0	0	—	—	0	—	
			7.5	Cort.	600	14		....	....	0	0	0	0	0	—	—	0	—	
			8.5	ACTH	350	14		....	....	0	0	0	0	0	—	—	0	—	living
			9.5	Cort.	900	21		....	....	0	0	0	0	0	—	*	0	—	(24.5+)
5.	M	3	5	Cort.	1,775	31	Amino-	Yes	3	*	*	*	*	*	—	*	†	4	
			6	ACTH	550	18	pterin	....	....	*	—	—	—	0	—	0	—	—	
			7	Cort.	150	6		Yes	3	†	—	—	—	*	—	0	—	—	
			8	Cort.	1,000	10		Yes	2	—	—	—	—	—	—	—	—	—	8.5
6.	M	4.5	1	ACTH	625	7	....	Yes	4	*	*	*	*	*	*	0	0	2	2.5
			1.5	Cort.	425	8		Yes	....	*	*	*	*	*	*	—	0		
7.	M	2	0.5	ACTH	675	15	....	....	....	*	*	0	0	0	0	—	—	—	
			1.0	Cort.	600	14		....	....	*	0	0	0	0	0	0	—	—	3.5
8.	M	16	8	ACTH	300	2	....	Yes	18	*	—	—	0	*	—	0	—	—	
			8	Cort.	2,950	18													9.0
9.	F	3	0.5	ACTH	1,430	42	....	Yes	10	*	—	—	—	—	—	—	—	—	4.0
10.	M	11	1.5	ACTH	1,700	14	....	Yes	1	*	*	—	*	*	*	0	†	2	
			2.5	Cort.	400	4		Yes	3	—	—	—	—	—	—	—	—	—	2.5
11.	M	5	2	ACTH	4,700	28	Chicken-	Yes	1	*	*	*	*	0	*	*	*	5	
			4	Cort.	2,275	25	pox	....	2	*	—	—	—	—	*	—	—	—	6.0
12.	M	3	1.5	ACTH	1,000	10	....	....	3	—	—	—	—	*	—	—	—	—	2.0
13.	F	5	6	ACTH	900	8	Melamine	Yes	1	—	—	—	—	0	—	0	—	—	6.5
14.	M	2	7.5	ACTH	187	4	....	Yes	3	—	—	—	—	—	—	—	—	—	7.5
15.	M	4	2.5	Cort.	1,150	14	X-ray	Yes	3	*	†	—	—	*	—	—	—	—	3.0

Symbols: * = definite effect; † = equivocal effect; — = no effect; 0 = not present or not determined.

Three patients were treated for leukemia with other agents before hormonal therapy was given. One of them (Case 3) received a course of aminopterin (4-aminopteroyl-glutamic acid) one month before treatment with cortisone. Another (Case 13) had had three courses of trisethylene melamine (trisethylene-imino-*s*-triazine), and one (Case 15) had had two courses of roentgen therapy necessitated by the presence of a large mediastinal mass that embarrassed respiration.

In Case 6, the patient was treated with 5 mg. of nitrogen mustard (methyl-bis-betachloroethyl amine) after completion of the hormone therapy, also because of a mediastinal mass. The excellent clinical remission in Case 11 was observed following the onset of chickenpox; the hormones were used primarily in an attempt to prolong the remission presumed to have been due to the acute infectious disease.

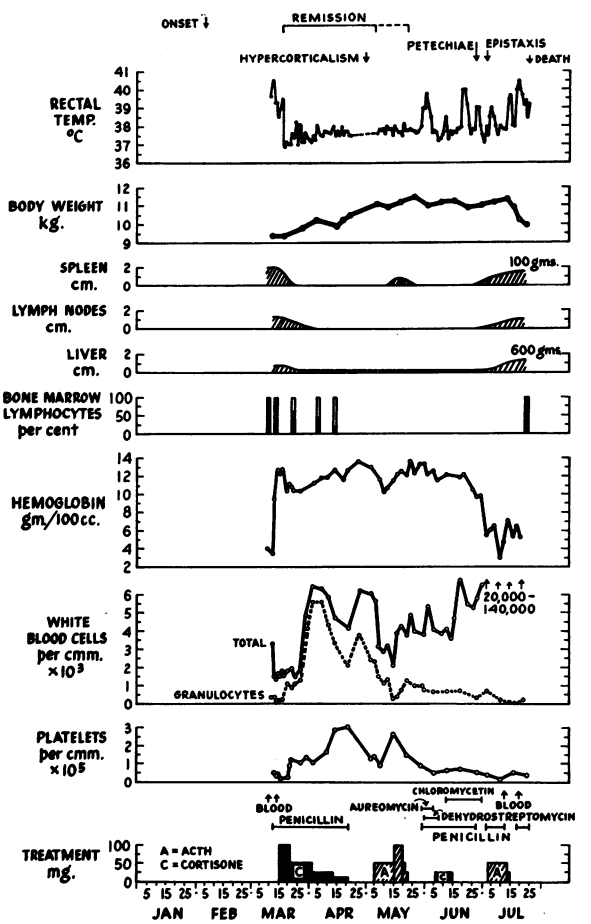
RESULTS

Subjective improvement during hormone therapy was observed in 12 of the 15 patients. Evidence of such improvement included more normal activity, expressions of a sense of well-being, reduced irritability, and better general appearance. This was accompanied by a great increase in appetite, to be anticipated with the use of the agents, and reduction of temperature to normal levels in nine cases.

Objective evidence of clinical improvement was observed in seven patients. Such evidence included significant and sustained reduction in the size of the spleen, liver and lymph nodes, and a significant decrease in the absolute number of leukemic cells in the peripheral blood and/or the bone marrow with a concomitant rise in the normal blood elements. A pronounced increase in the number of platelets was observed in two patients, and a slight transient rise in three others.

The typical, almost complete remission in Case 1 is detailed in Chart 1. A dramatic drop in temperature and reduction in the size of spleen, lymph nodes and the liver occurred within a week after the initiation of treatment with cortisone. There was a rise in the number of granulocytes in the peripheral blood, and, somewhat later, in the number of platelets. At the same time, the number of lymphoblasts and abnormal lymphocytes in the bone marrow dropped from 98 per cent to 25 per cent of the total number of leukocytes. The effects were sustained for approximately seven weeks, and were partially achieved for another two weeks following the second course with corticotropin. Subsequent hormonal therapy was without avail, and leukemic leukocytosis and hemorrhagic diathesis developed. The total duration of the disease, from clinical onset, was six months.

CHART 1



Results of treatment with cortisone and corticotropin in the case of an 18-month-old boy with lymphogenous leukemia.

The beneficial effects in five patients were transient, lasting two to four weeks. In two patients the remissions lasted five and sixteen weeks, respectively. Favorable response was noted in three of six patients with subleukemic disease, in three of five patients with frank leukemia, and in one of four patients who had both leukopenia and leukocytosis during the course of the illness.

The initial course of treatment was with cortisone in five cases, with three remissions, and with corticotropin in ten cases, with four remissions. In the plan of treatment these two agents were used alternately, with a rest period of seven to ten days between courses. Thus, nine children received a second course of the hormones; of four patients treated with corticotropin, two had remissions, but no further remissions occurred in five patients that received a second course with cortisone. Five children, including four who had responded to the first course of treatment, received four courses of the two hormones, but no

remissions were observed with either the third or the fourth course.

During the course of treatment the usual signs and symptoms of hypercorticalism were observed in ten of the fifteen children. These consisted of rounding of the face, and enlargement of the abdomen. Edema of the extremities was noted in these patients, and was controlled by reduction in the dose of the hormones, further decrease of sodium intake and supplementation of potassium chloride. Transient elevation of blood pressure developed in two patients. None of the complications was serious.

The mean survival of all fifteen patients after the onset of symptoms attributable to the disease, including the single patient still living, was 6.8 ± 1.4 months. If the patient with chronic leukemia is not considered, the mean survival was 5.5 ± 0.9 months. The median survival, as determined by interpolation of the graphed data on all fifteen patients, was 4.8 months. Survival among seven patients who responded to treatment was from 2.5 to 11 months, and the average was 5.9 months. Survival among seven patients who had no objective response was from 2 to 9 months, and the average 5.1 months. Excluding the five patients who received x-ray or radiomimetic chemicals and the patient who had chickenpox, the mean survival of the remaining nine patients was 5.6 months.

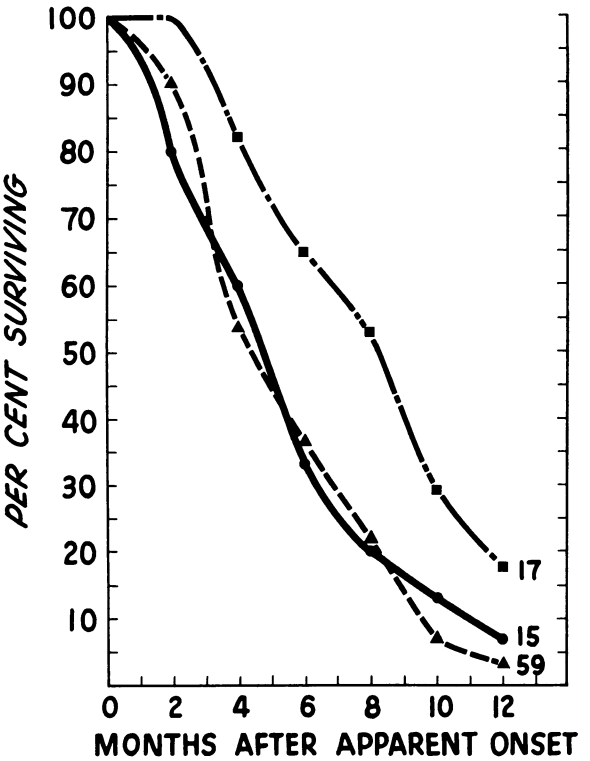
DISCUSSION

The results relative to duration of life in this group of patients were compared with a previous base-line study on the duration of life in 76 children with lymphogenous leukemia.[1] In that study it was noted that among 59 patients who received no treatment, or treatment with x-ray or blood transfusions only, the mean survival was 5.8 ± 0.5 months. Among seventeen patients who were treated with both antibiotics and blood transfusions, the average survival was 8.9 ± 1.2 months, a difference significant at the 2 per cent level. One of this group survived for 23 months; if this case is excluded, a mean of 8.0 ± 0.8 months is obtained. This mean is significantly different from the mean of the group of 59 cases at the 1 per cent level.

The survival of fifteen children treated with corticotropin or cortisone was 6.8 ± 1.4 months, or 5.5 ± 0.9 months if the patient with chronic leukemia who is still living is not considered. Neither of these means is significantly different from the mean of the 59 patients. If the mean on 14 children is compared with the mean on 16 children treated with antibiotics and blood transfusions, but excluding the case of longest survival, a difference significant at the 1 per cent level is obtained (5.5 ± 0.9 against 8.0 ± 0.8).

These data are graphically presented in Chart 2. It

CHART 2



Duration of life in children with lymphogenous leukemia. Square dots, 17 children treated with antibiotics and blood transfusions; triangular dots, 59 children treated with x-ray, blood transfusions or receiving no treatment; solid line, 15 children treated with cortisone and corticotropin.

is quite clear that the duration of life in children with lymphogenous leukemia treated with corticotropin and with cortisone is the same as in the children who do not receive these agents. The clinical remissions, therefore, are not reflected in a longer duration of life. Since 12 of the 15 children who received the hormones also received antibiotics and blood transfusions, it could have been anticipated that the duration of life would have been closer to the mean of 8.9 months than the 6.8 months actually observed.

The analysis of the results on this small group of patients indicates that the effects of corticotropin and of cortisone in childhood leukemia were palliative, and that the duration of life was not increased by the use of these hormones.

Laguna Honda Home.

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